LIMBITROL - chlordiazepoxide and amitriptyline tablet, film coated
LIMBITROL DS - chlordiazepoxide and amitriptyline tablet, film coated
Valeant Pharmaceuticals International

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Chlordiazepoxide and Amitriptyline Hydrochloride Tablets or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Chlordiazepoxide and Amitriptyline Hydrochloride Tablets is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)
Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Limbitrol combines for oral administration, chlordiazepoxide, an agent for the relief of anxiety and tension, and amitriptyline, an antidepressant. It is available in DS (double strength) white, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt); and in blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Each tablet also contains corn starch, hydroxypropyl cellulose, hyproxypropyl cellulose, hyproxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone and propylene glycol; Limbitrol tablets contain the following colorant system-FD&C Blue No. 1, aluminum lake and titanium dioxide. Limbitrol DS tablets contain titanium dioxide.
Chlordiazepoxide is a benzodiazepine with the formula 7-chloro-2-(methyl-amino)-5-phenyl-*3H*-1,4- benzodiazepine 4-oxide. It is a slightly yellow crystalline material and is insoluble in water. The molecular weight is 299.76.
Amitriptyline is a dibenzocycloheptadiene derivative. The formula is 10,11-dihydro-*N*,*N*-dimethyl-5H-dibenzo [a,d] cycloheptene-#^{5y}-propylamine hydrochloride. It is a white or practically white crystalline compound that is freely soluble in water. The molecular weight is 313.87.

ACTIONS

Both components of Limbitrol exert their action in the central nervous system. Extensive studies with chlordiazepoxide in many animal species suggest action in the limbic system. Recent evidence indicates that the limbic system is involved in emotional response. Taming action was observed in some species. The mechanism of action of amitriptyline in man is not known, but the drug appears to interfere with the reuptake of norepinephrine into adrenergic nerve endings. This action may prolong the sympathetic activity of biogenic amines.

INDICATIONS

Limbitrol is indicated for the treatment of patients with moderate to severe depression associated with moderate to severe anxiety. The therapeutic response to Limbitrol occurs earlier and with fewer treatment failures than when either amitriptyline or chlordiazepoxide is used alone.
Symptoms likely to respond in the first week of treatment include: insomnia, feelings of guilt or worthlessness, agitation, psychic and somatic anxiety, suicidal ideation and anorexia.

CONTRAINDICATIONS

Limbitrol is contraindicated in patients with hypersensitivity to either benzodiazepines or tricyclic antidepressants. It should not be given concomitantly with a monoamine oxidase inhibitor. Hyperpyretic crises, severe convulsions and deaths have occurred in patients receiving a tricyclic antidepressant and a monoamine oxidase inhibitor simultaneously. When it is desired to replace a monoamine oxidase inhibitor with Limbitrol, a minimum of 14 days should be allowed to elapse after the former is discontinued. Limbitrol should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.
This drug is contraindicated during the acute recovery phase following myocardial infarction.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant

medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicidesoccurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions forChlordiazepoxide and Amitriptyline Hydrochloride Tablets should be written for the smallest quantityof tablets consistent with good patient management, in order to reduce the risk of overdose.Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatrichistory, including a family history of suicide, bipolar disorder, and depression. It should benoted that Chlordiazepoxide and Amitriptyline Hydrochloride Tablets is not approved for use intreating bipolar depression.

General

Because of the atropine-like action of the amitriptyline component, great care should be used in treating patients with a history of urinary retention or angle-closure glaucoma. In patients with glaucoma, even average doses may precipitate an attack. Severe constipation may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia and prolongation of conduction time. Myocardial infarction and stroke have been reported in patients receiving drugs of this class.

Because of the sedative effects of Limbitrol, patients should be cautioned about combined effects with alcohol or other CNS depressants. The additive effects may produce a harmful level of sedation and CNS depression.

Patients receiving Limbitrol should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Usage in Pregnancy
Safe use of Limbitrol during pregnancy and lactation has not been established. Because of the chlordiazepoxide component, please note the following:
An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.
Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE section.)

PRECAUTIONS

General
Use with caution in patients with a history of seizures.
Close supervision is required when Limbitrol is given to hyperthyroid patients or those on thyroid medication.
The usual precautions should be observed when treating patients with impaired renal or hepatic function.
Patients with suicidal ideation should not have easy access to large quantities of the drug. The possibility of suicide in depressed patients remains until significant remission occurs.

Essential Laboratory Tests
Patients on prolonged treatment should have periodic liver function tests and blood counts.

Drug and Treatment Interactions
Because of its amitriptyline component, Limbitrol may block the antihypertensive action of guanethidine or compounds with a similar mechanism of action.

Drugs Metabolized by P450 2D6:
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7% to 10% of caucasians are so called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the type 1c antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).
Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.
The effects of concomitant administration of Limbitrol and other psychotropic drugs have not been evaluated. Sedative effects may be additive.
Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants and benzodiazepines, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine (Tagamet).
The drug should be discontinued several days before elective surgery.
Concurrent administration of ECT and Limbitrol should be limited to those patients for whom it is essential.

Pregnancy
See WARNINGS section.

Nursing mothers
It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug, since many drugs are excreted in human milk.

Pediatric use
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS-Clinical Worsening and Suicide Risk).
Anyone considering the use of Chlordiazepoxide and Amitriptyline Hydrochloride Tablets in a child or adolescent must balance the potential risks with the clinical need.

Geriatric use
In elderly and debilitated patients it is recommended that dosage be limited to the smallest effective amount to preclude the development of ataxia, oversedation, confusion or anticholinergic effects.
Of the total number of subjects in clinical studies of Limbitrol, 74 individuals were 65 years and older. An additional 34 subjects were between 60 and 69 years of age. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
The active ingredients in Limbitrol are known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.
Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Limbitrol and observed closely.
Clinical studies of Limbitrol did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Information for patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with LIMBITROL and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for LIMBITROL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.
Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking LIMBITROL.

Clinical Worsening and Suicide Risk
Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS
Adverse reactions to Limbitrol are those associated with the use of either component alone. Most frequently reported were drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Other side effects occurring less commonly included vivid dreams, impotence, tremor, confusion and nasal congestion. Many symptoms common to the depressive state, such as anorexia, fatigue, weakness, restlessness and lethargy, have been reported as side effects of treatment with both Limbitrol and amitriptyline.
Granulocytopenia, jaundice and hepatic dysfunction of uncertain etiology have also been observed rarely with Limbitrol. When treatment with Limbitrol is prolonged, periodic blood counts and liver function tests are advisable.
Note: Included in the listing which follows are adverse reactions which have not been reported with Limbitrol. However, they are included because they have been reported during therapy with one or both of the components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

DRUG ABUSE AND DEPENDENCE

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of chlordiazepoxide. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Withdrawal symptoms (e.g., nausea, headache and malaise) have also been reported in association with abrupt amitriptyline discontinuation. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addictionprone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving chlordiazepoxide or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE*

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.
Manifestations: Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.
Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia or any of the symptoms listed under ADVERSE REACTIONS.
Management: General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. ***There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination.*** Monitoring of plasma drug levels should not guide management of the patient.
Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.
Cardiovascular: A maximal limb-lead QRS duration of ³ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.56, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a pCO2< 20mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type ***1A and 1C*** antiarrhythmics are generally contraindicated (eg, quinidine, disopyramide and procainamide).
In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.
CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). ***Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies,*** and then only in consultation with a poison control center.
Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.
Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

*Poisindex® Toxicologic Management. Topic: Antidepressants, Tricyclic. *Micromedex Inc.* Vol. 85.

Chlordiazepoxide Overdosage
Manifestations of benzodiazepine overdosage include somnolence, confusion, coma and diminished reflexes. Dialysis is of limited value. There have been occasional reports of excitation in patients following benzodiazepine overdosage; if this occurs, barbiturates should not be used. Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section). Since Limbitrol contains amitriptyline, it is important to note that use of the benzodiazepine antagonist flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

DOSAGE AND ADMINISTRATION
Optimum dosage varies with the severity of the symptoms and the response of the individual patient. When a satisfactory response is obtained, dosage should be reduced to the smallest amount needed to maintain the remission. The larger portion of the total daily dose may be taken at bedtime. In some patients, a single dose at bedtime may be sufficient. In general, lower dosages are recommended for elderly patients.
Limbitrol DS (double strength) Tablets are recommended in an initial dosage of 3 or 4 tablets daily in divided doses; this may be increased to 6 tablets daily as required. Some patients respond to smaller doses and can be maintained on 2 tablets daily.
Limbitrol Tablets in an initial dosage of 3 or 4 tablets daily in divided doses may be satisfactory in patients who do not tolerate higher doses.

HOW SUPPLIED
Limbitrol DS (double strength) Tablets are available as white, film-coated, biconvex tablets containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) in bottles of 100 (NDC 0187-3806-10). Each tablet is engraved “V 3806” on one side.
Limbitrol Tablets are available as blue, film-coated, biconvex tablets containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) in bottles of 100 (NDC 0187-3805-10). Each tablet is engraved “V 3805” on one side.
Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F). Store in a dry place.

SUPPLEMENTAL PATIENT MATERIAL

Medication Guide About Using Antidepressants in Children and Teenagers
What is the most important information I should know if my child is being prescribed an antidepressant?
Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:
1. There is a risk of suicidal thoughts or actions

2. How to try to prevent suicidal thoughts or actions in your child

3. You should watch for certain signs if your child is taking an antidepressant

4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions
Children and teenagers sometimes think about suicide, and many report trying to kill themselves.
Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called suicidality or being suicidal.
A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.
For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with
• Bipolar illness (sometimes called manic-depressive illness)

• A family history of bipolar illness

• A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.
2. How to Try to Prevent Suicidal Thoughts and Actions
To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child’s life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.
Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide.

In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*Prozac® is a registered trademark of Eli Lilly and Company

*Zoloft® is a registered trademark of Pfizer Inc.

*Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Valeant Pharmaceuticals International
3300 Hyland Ave., Costa Mesa, CA 92626 U.S.A.

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